

REMARKS

Claims 1, 5, 19-20, 22-43, 55, 56 and 58-59 were pending in the present application. Claims 27-29, 32-33 and 40-43 are withdrawn from consideration. With this amendment, Applicants have amended claims 1, 26, 35, 36, 38, 39, 40, 55 and 59, for purposes of clarity. Applicants have canceled claims 41 and 56 without prejudice. Applicants have also added new claims 66-71.

Support for the amendments and new claims is found in the application as filed, as follows:

Support for the amendments to claim 1 may be found *inter alia* on page 5, line 9 to page 6, line 20; page 15, lines 20-24; page 16, lines 10 and 16-19; page 18, lines 1-32; and page 45, lines 6-9 of the subject application.

Support for the amendments to claim 26 may be found *inter alia* on page 5, line 9 to page 6, line 20 of the subject application.

Support for the amendments to claim 35 may be found *inter alia* on page 5, line 9 to page 6, line 20 of the subject application.

Support for the amendments to claim 36 may be found *inter alia* on page 5, line 9 to page 6, line 20 of the subject application.

Support for the amendments to claim 38 may be found *inter alia* on page 5, line 9 to page 6, line 20 of the subject application.

Support for the amendments to claim 39 may be found *inter alia* on page 5, line 9 to page 6, line 20 of the subject application.

Support for the amendments to withdrawn claim 40 may be found *inter alia* on page 5, line 9 to page 6, line 20 of the subject application.

Support for the amendments to claim 55 may be found *inter alia* on page 5, line 9 to page 6, line 20 of the subject application.

Support for new claim 66 may be found *inter alia* on page 5, line 9 to page 6, line 20; page 15, lines 20-24; page 16, lines 10 and 16-19; page 18, lines 1-32; and page 45, lines 6-9 of the subject application.

Support for new claim 67 may be found *inter alia* on page 5, line 9 to page 6, line 20; page 15, lines 20-24; page 16, lines 10 and 16-19; page 18, lines 1-32; page 45, lines 6-9; and original claim 36 of the subject application.

Support for new claim 68 may be found *inter alia* on page 5, line 9 to page 6, line 20; page 15, lines 20-24; page 16, lines 10 and 16-19; page 18, lines 1-32; page 45, lines 6-9; and original claim 26 of the subject application.

Support for new claim 69 may be found *inter alia* on page 5, line 9 to page 6, line 26; page 15, lines 20-24; page 16, lines 10 and 16-19; page 18, lines 1-32; page 45, lines 6-9; and original claim 30 of the subject application.

Support for new claim 70 may be found *inter alia* on page 68, line 31 to page 69, line 10 of the subject application.

Support for new claim 71 may be found *inter alia* on page 70, lines 1-10, page 72, lines 8-29, and page 73, lines 10-33 of the subject application.

These amendments are made without prejudice. Applicants reserve the right to prosecute the deleted subject matter in related applications. Applicants believe that no new matter is added by these amendments.

After entry of this amendment, claims 1, 5, 19-20, 22-40, 42-43, 55, 58-59 and 66-71 will be pending.

Entry of the foregoing amendments and consideration of these remarks are respectfully requested.

Claim Rejections - 35 U.S.C. § 112

Claims 1, 5, 19-20, 22-26, 30-31, 34-39, 55-56 and 58-59 were rejected under 35 U.S.C. 112, first paragraph, as allegedly being indefinite for failing to comply with the written description requirement. Specifically, the Examiner contends that in claim 1, at lines 26-27, the removal of the proviso “a is 1 unless A is proline, B is histidine, C is serine and b is 0 when a is 0; and R^2 is $(CH_2)_mS(O)_nR^5$ or $(CH_2)_mS(O)_nS(O)_oR^5$ unless b, x, y and z are 1” is deemed new matter because the instant specification (see pages 3-4), as well as original claim 1 do not properly support the concept of species without that proviso being incorporated within the compounds encompassed by formula (I). The Examiner stated that the instant specification (including the original claims) discloses compounds of Formula (I) with the proviso that “a is 1 unless A is proline, B is histidine, C is serine and b is 0 when a is 0; and R_2 is $(CH_2)_mS(O)_nR_5$ or

$(CH_2)_mS(O)_nS(O)_oR_5$ unless b, x, y and z are 1". The Examiner alleged that by removing the limitations stated above, the claims are broadened with no support from the specification. The Examiner suggested that the limitations set forth in the cited claims be appropriately reincorporated into the claims cited above to overcome this rejection. The Examiner further stated that all other cited claims depend directly or indirectly from rejected claims and are, therefore, also rejected under U.S.C. § 112, first paragraph for the reasons set forth above.

In response, Applicants respectfully disagree with the Examiner's rejection. Claim 1 has been further amended to delete the proviso phrase "with the proviso that: R^5 is not methyl when m is 1." Claim 1 as thus amended lacking any proviso is fully supported in the application as filed. Specifically, the following table outlines the support in the application as filed for claim 1 as amended:

| Element | Support |
|---|--|
| formula (I) | Page 15, line 20-25 and page 45, lines 6-9 |
| a, b, x, y and z are 1 | Page 18, lines 17-18 |
| A is proline; B is histidine; C is serine | Page 18, lines 16-17 |
| R^1 is acyl, substituted acyl, oxycarbonyl and substituted oxycarbonyl; | Page 18, line 17 |
| R^2 is alkyl | Page 18, line 19 |
| R^2 is $-(CH_2)_mS(O)_nR^5$ or $-(CH_2)_mS(O)_n-S(O)_oR^5$; | Page 18, lines 1-2 |
| m is 1 or 2 | Page 18, line 18 |
| n and o are independently 0, 1 or 2 | Page 18, lines 22-32 |
| R^3 is $-CH_2CONH_2$; | Page 18, line 19 |
| R^4 is NH_2 ; | Page 18, line 18 |
| R^5 is alkyl ethyl, propyl, butyl, alkenyl, alkynyl, substituted alkyl, acyl, substituted acyl, aryl, substituted aryl, arylalkyl, | Page 18, lines 21-25 (R^5 is alkyl, substituted alkyl, acyl, substituted acyl, arylalkyl, oxycarbonyl or substituted oxycarbonyl) |

| Element | Support |
|---|--|
| substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, oxycarbonyl or substituted oxycarbonyl | <p>Page 18, lines 29-32 (R^5 is acyl)</p> <p>Page 5, line 9 to page 6, line 20 (alkyl is ethyl, propyl, a butyl, alkenyl, alkynyl)</p> <p>Page 16, line 16-19 (R^5 is substituted alkyl, acyl, substituted acyl, aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroalkyl, substituted heteroalkyl, heteroaryl, substituted heteroaryl, heteroarylalkyl, substituted heteroarylalkyl, oxycarbonyl or substituted oxycarbonyl)</p> |

In addition to the above showing that claim 1 as amended is fully supported by the specification, the applicants maintain that consideration of the claims depending on claim 1, as filed, shows that the specification contemplates that species without those provisos are within the scope of claim 1. Thus, it is apparent that inclusion of the provisos in original claim 1 was an editorial error, since these provisos are inconsistent with the originally filed dependent claims. For example, original claims 36 and 56 are not possible with the proviso " R^5 is not methyl when m is 1." Claim 36 as originally filed recited "wherein R^5 is methyl...". Claim 36 depended indirectly on claim 34 which recited "m is 1," which in turn depended indirectly on original claim 1. Similarly, claim 56 as originally filed recited "wherein R^5 is methyl" and depended indirectly on claim 55 which recited "m is 1," which depended indirectly on original claim 1. These two originally filed claims were therefore taught to be within the scope of claim 1, but are inconsistent with the proviso " R^5 is not methyl when m is 1."

Applicants point out that the specification as filed also shows that species inconsistent with the other provisos of claim 1 were also contemplated as within the scope of claim 1, since the other provisos of original claim 1 are also inconsistent with originally filed dependent claims. For example, original claim 1 also contained the second proviso "a is 1 *unless* A is proline, B is histidine, C is serine and b is 0 when a is 0" (emphasis added). Claim 2 as originally filed, which depended on original claim 1, recited "wherein A is proline, B is

histidine, C is serine and R^3 is $-\text{CH}_2\text{CONH}_2$.” However, in accordance with the proviso of claim 1; “a” of original claim 2 must necessarily be “0”. This proviso then dictates that “b” of original claim 2 must also be “0” and “ R^3 ,” therefore, does not exist. This proviso is clearly inconsistent with original claim 2. Therefore, it is apparent that the proviso is an editorial error.

The specification as filed also clearly teaches that species inconsistent with the third proviso of claim were contemplated within the scope of claim 1. Thus, claim 25 as originally filed is inconsistent with the proviso “ R^2 is $-(\text{CH}_2)_m\text{S}(\text{O})_n\text{R}^5$ or $-(\text{CH}_2)_m\text{S}(\text{O})_n-\text{S}(\text{O})_o\text{R}^5$ unless b, x, y and z are 1” (emphasis added) of original claim 1. Original claim 25 recited “ R^2 is $-(\text{CH}_2)_m\text{S}(\text{O})_n\text{R}^5$ ” and depended indirectly on original claim 21 which recited “a, b, x, y and z are 1” and depended indirectly on claim 1. However, if in original claim 25, “b, x, y and z are 1”, then the third proviso dictates that “ R^2 ” cannot be “ $-(\text{CH}_2)_m\text{S}(\text{O})_n\text{R}^5$.” This proviso clearly is inconsistent with original claim 25. Thus, it is apparent that the third proviso also must be an editorial error.

The specification describes numerous embodiments of the invention (see page 15, line 20 to page 19, line 16 of the subject application). Clearly not all of these embodiments conform with the limitations set forth in the provisos listed on page 16, line 26 to page 17, line 2 of the subject application. Indeed, inclusion of these deleted provisos in claim 1 would exclude from its scope many of the compounds described in the specification and in the claims (including claims ultimately depending on claim 1, as discussed above). For example, the proviso “ R^5 is not methyl when m is 1” would exclude compound 11 of Figure 2. Furthermore, the proviso “a is 1 unless A is proline, B is histidine, C is serine and b is 0 when a is 0” would exclude all of the disclosed pentapeptide compounds of the subject application (e.g. compounds 1-6 of Figure 1, compounds 7-12 of Figure 2, compounds 12-18 of Figure 3 and compounds 30-35 of Figure 5). Finally, the proviso “ R^2 is $-(\text{CH}_2)_m\text{S}(\text{O})_n\text{R}^5$ or $-(\text{CH}_2)_m\text{S}(\text{O})_n-\text{S}(\text{O})_o\text{R}^5$ unless b, x, y and z are 1” excludes pentapeptides where the 4th amino acid contains a side chain with sulfur (see Examples 10-13, page 60, line 1 to page 61, line 20; Example 18, page 62, line 27 to page 63, line 5; Examples 20-23, page 63, line 17 to page 65, line 9; and Examples 29-51, page 67, line 1 to page 75, line 31 of the subject application). These exclusions clearly were not intended by Applicants and thus, it is apparent that the provisos were not intended to limit claim 1.

As demonstrated above, amended claim 1 is fully supported by the specification and does not introduce new matter. Accordingly, the rejection under 35 U.S.C. § 112 has been obviated.

Claim Rejections - 35 U.S.C. § 103

The Examiner rejected claims 1, 5, 19-20, 22-24, 26, 35-39, 55-56 and 58-59 under 35 U.S.C. 103(a) as allegedly being unpatentable over U.S. Patent No. 6,001,965 (“Livant”). On pages 5-6 of the November 15, 2006 Office Action, the Examiner stated:

Livant teaches a high activity anti-angiogenic compound Ac-Pro-His-Ser-Cys-Asn-NH₂, (e.g. column 26, 27-40, Figures and Examples 9-13). Livant teaches that substituting the fourth amino acid position for homo-cysteine to produce Ac-Pro-His-Ser-homoCys-Asn-NH₂ (Example 11) maintains a strong inhibitory effect and also teaches that the Cys position may also be occupied by a methionine (e.g. column 3, lines 16-40). Livant does not expressly teach the compound Ac-Pro-His-Ser-Met-Asn-NH₂. It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of Ac-Pro-His-Ser-Cys-Asn-NH₂ of Livant by substituting the cysteine for a methionine as taught by Livant. The skilled artisan would have been motivated to do so because Livant teaches that such amino acid position may be substituted by methionine (e.g. column 3, lines 16-40). There would have been a reasonable expectation of success, given that the analogous substitution of cysteine for homo-cysteine at that same position produces a strong inhibitory effect (Example 11) and that homo-cysteine and methionine chemically differ only by substitution of a hydrogen for a methyl group. The adjustment of particular conventional working conditions (e.g., selecting specific D/L stereochemistry, e.g., column 3, lines 39-40) within such compounds is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Livant does not teach or suggest the claimed pentapeptides

In response, Applicants point out that all of the rejected claims of the subject application specify N-terminal modified and C terminal amidated pentapeptides with a side chain substitution on the 4th amino acid that are not taught or suggested by Livant.

For example, claim 1 as amended recites “R² is alkyl, -(CH₂)_mS(O)_nR⁵ or -(CH₂)_mS(O)_n-S(O)_oR⁵; m is 1 or 2; n and o are independently 0, 1 or 2...” to define the side chain substitution of the 4th amino acid of the pentapeptides. Livant provides no teaching or suggestion of pentapeptides with a side chain substitution on the 4th amino acid that is alkyl or contains the “-S-S-” moiety or a S that is oxidized. Moreover, Livant provides no motivation to

modify the side chains on the 4th amino acid of the pentapeptides therein to arrive at pentapeptides with a side chain substitution on the 4th amino acid that is alkyl or contains the “-S-S-” moiety or a S that is oxidized (i.e., the pentapeptides of amended claim 1).

Furthermore, Applicants have amended claim 1 to recite “R⁵ is ethyl, propyl, butyl, alkenyl, alkynyl ...” Livant provides no teaching or suggestion of pentapeptides with side chain substitution on the 4th amino acid where the sulfur atom is distally substituted by any thing other than hydrogen or methyl.

In Example 11 of Livant (see column 24, lines 26-42), the two pentapeptides disclosed, which are referred to as SEQ ID NO 85 and SEQ ID NO 86, differ only in the amino acid at position 4. SEQ ID NO 86 has a cysteine at position 4, while SEQ ID NO 85 has a homo cysteine at position 4. However, both cysteine and homocysteine have a side chain ending with a sulfhydryl group (SH). Livant teaches that both peptides demonstrate similar inhibitory effects in inhibiting prostate cancer cell invasion (see Livant at column 24, lines 26-44). However, there is no teaching or suggestion that pentapeptides with amino acids in the 4th position that have side chains with substitution on S other than H would demonstrate similar inhibitory effects.

Although Livant discloses a generic sequence X₁X₂X₃X₄X₅ which can have methionine in the 4th position, there is no suggestion to modify the side chain of the met residue and there is no discussion of the effect of this substitution on the activity of the peptide. In fact, Livant does not teach anything about the structure activity relationships required for the side chain of the fourth amino acid of the pentapeptide other than the aforementioned similarity in activity between cysteine and homocysteine containing peptides.

Therefore, the pentapeptides of amended claim 1 would not be obvious in view of the disclosure of Livant.

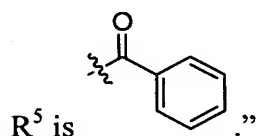
Applicants have introduced new claims 66-67. New claim 66 recites “R² is -(CH₂)_mS(O)_nR⁵; m is 1 or 2; n is 1 or 2... R⁵ is methyl.” Applicants point out that this claim requires that the sulfur atom of the R² side chain be oxidized. As noted above, Livant provides no teaching or suggestion of pentapeptides with side chain substitution on the 4th amino acid where the sulfur atom is oxidized as required by new claim 66. Furthermore, Livant provides no motivation to modify the side chains on the 4th amino acid pentapeptides to arrive at the pentapeptides with oxidized sulfur moieties as required by new claim 66. Therefore, the pentapeptides of new claim 66 would not be obvious in view of the disclosure of Livant.

New claim 67 recites “R² is -(CH₂)_mS(O)_n-S(O)_oR⁵; m is 1; n and o are 0... R⁵ is methyl.” As noted above, Livant provides no teaching or suggestion of pentapeptides with side chain substitution on the 4th amino acid containing the “-S-S-” moiety as required by new claim 67. Furthermore, Livant provides no motivation to modify the side chains on the 4th amino acid pentapeptides to arrive at the pentapeptides containing the “-S-S-” moiety as required by new claim 67. Therefore, the pentapeptides of new claim 67 would not be obvious in view of the disclosure of Livant.

New claim 68 recites “R² is -(CH₂)_mS(O)_nR⁵; m is 1; n is 0;... R⁵ is methyl.” Livant provides no teaching or suggestion of a pentapeptide with side chain substitution on the 4th amino acid containing only one “CH₂” group between the peptide backbone and the “S” when the “S” is capped with a methyl group. Therefore, the pentapeptide of new claim 68 would not be obvious in view of the disclosure of Livant.

New claim 69 recites “R² is -(CH₂)_mS(O)_nR⁵; m is 1; n is 0;... R⁵ is acetyl.” Livant provides no teaching or suggestion of a pentapeptide with side chain substitution on the 4th amino acid containing only one “CH₂” group between the peptide backbone and the “S” when the “S” is capped with an acetyl group. Therefore, the pentapeptide of new claim 69 would not be obvious in view of the disclosure of Livant.

New claim 70 recites “R² is -(CH₂)_mS(O)_nR⁵; m is 1; n is 0;...



On page 2 of the November 15, 2006 Office Action, the Examiner acknowledged that this structure has been found to be free of the prior art. Applicants agree since Livant provides no teaching or suggestion of a pentapeptide with side chain substitution on the 4th amino acid containing “S-benzoyl.” Therefore, the pentapeptide of new claim 70 would not be obvious in view of the disclosure of Livant.

Moreover, effects of the substitution of the side chain of the 4th amino acid of the pentapeptides of the claimed invention are unpredictable. Compounds of the claimed invention exhibit unexpected results which are objective evidence of nonobviousness.

To establish invalidity under 35 U.S.C. § 103, certain factual predicates are required before the legal conclusion of obviousness or nonobviousness can be reached. The underlying factual determinations to be made are (1) the scope and

content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of non-obviousness, such as commercial success, long-felt but unsolved need, failure of others, copying, and unexpected results. *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S.Ct. 684, 15 L.Ed.2d 545, 148 USPQ 459, 467 (1966).

Apple Computer, Inc. v. Articulate Systems, Inc., 234 F.3d 14, 26 (Fed. Cir. 2000). The unexpected results exhibited by the compounds of the claimed invention are described in the Declaration of Dr. Andrew P. Mazar Under 37 C.F.R. § 1.132 (“Dr. Mazar’s Declaration”) submitted herewith.

The Examiner’s attention is directed to Dr. Mazar’s Declaration where the biological activities (inhibition of tumor growth) of numerous peptides within the scope of the subject claims are disclosed. The most active compound, Ac-PHSC(Me)N-NH₂, which has a side chain of CH₂SCH₃ on the 4th amino acid, unexpectedly inhibited tumor growth greater than 3 times better than Ac-PHSCN-NH₂ (SEQ 86 of Livant), which has a side chain of CH₂SH (see paragraph 6, Table 1 of Dr. Mazar’s Declaration). New claim 68 is directed to this compound. Another compound with an unexpectedly high degree of activity is the S-acetyl compound (Ac-PHSC(acetyl)N-NH₂) which was almost as active as the Ac-PHSC(Me)N-NH₂ compound and inhibited tumor growth over 2 times better than Ac-PHSCN-NH₂. New claim 69 is directed towards this compound. Both of these results were unexpected (see paragraph 7 of Dr. Mazar’s Declaration). One skilled in the art would have no expectation from the teaching of Livant that an improvement of 2-3 x in the inhibition of tumor growth could be achieved with the substitution of SH by SCH₃ or S-acetyl.

Furthermore, Dr. Mazar states that the data provided in Dr. Mazar’s Declaration show the lack of predictability around the substitution pattern of the side chain of the 4th amino acid of the pentapeptides (see paragraph 7 of Dr. Mazar’s Declaration). As described by Dr. Mazar, other alkyl substitutions on the S of the side chain of the 4th amino acid produced pentapeptides which were much less capable than Ac-PHSC(Me)N-NH₂ or Ac-PHSCN-NH₂, (SEQ 86) at inhibiting the growth of tumors. For example, the S-t-butyl compound (Ac-PHSC(t-Butyl)N-NH₂) and the S-(CH₂)OCH₃ compound (Ac-PHSC(2-methoxyethyl)N-NH₂) are much less active than either the Ac-PHSC(Me)N-NH₂ or Ac-PHSCN-NH₂ compounds. Moreover, other acyl substituted compounds are also much less capable of inhibiting tumor growth. The S-pivoyl compound (Ac-PHSC(pivoyl)N-NH₂) had approximately the same activity as Ac-PHSCN-NH₂ and was much less active than Ac-PHSC(acetyl)N-NH₂, while the S-cyclohexanoyl (Ac-PHSC(cyclohexanoyl)N-NH₂),

S-benzoyl (Ac-PHSC(benzoyl)N-NH₂) and S-alloc (Ac-PHSC(alloc)N-NH₂) compounds were all much less active than either Ac-PHSCN-NH₂ or Ac-PHSC(acetyl)N-NH₂ (see paragraph 7 of Dr. Mazar's Declaration).

Also as shown in Dr. Mazar's Declaration, several compounds had similar activity to Ac-PHSCN-NH₂ (see Dr. Mazar's Declaration, paragraph 8), a result which could not have been predicted from Livant; these compounds are the subject of claim 71.

As further proof of the lack of predictability, data described by Dr. Mazar demonstrate that Ac-PHSCN-NH₂ (SEQ 86 by Livant) may have a different mechanism for inhibiting angiogenesis than Ac-PHSC(Me)N-NH₂ (the subject of present claim 68) (see Dr. Mazar's Declaration, paragraphs 9-13). While the inhibitory effect of Ac-PHSCN-NH₂ is reversed by the presence of the PKA inhibitor HA-1004, the inhibitory effect of Ac-PHSC(Me)N-NH₂, is surprisingly unaffected by the presence of HA-1004 thus suggesting distinct mechanisms for inhibiting angiogenesis between the two peptides (see paragraphs 9-13 of Dr. Mazar's Declaration).

For the above reasons, the claimed pentapeptides would not be obvious to one skilled in the art in view of Livant.

Accordingly, Applicants respectfully request the withdrawal of the rejection.

Double Patenting

The Examiner has provisionally rejected claims 1, 5, 19-20, 22-26, 30-31, 34-39, 55-56 and 58-59 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 64-67 of co-pending Application No. 10/722,843 (the "'843 application"). Specifically, the Examiner contends that the conflicting claims are not patentably distinct from each other because the instantly claimed invention and the invention claimed in the '843 application are both drawn to a genus of compounds which contain overlapping subject matter. The Examiner further contends that the instantly claimed broad formula (I) of the instant application encompasses and/or is encompassed by the claimed broad formula of the '843 application. Applicants respectfully disagree.

The legal standard for an obviousness-type double patenting rejection requires a comparison of what is *claimed* in the earlier patent, not what was disclosed in the specification of the earlier patent. See *e.g.*, *General Foods, Inc. v. Studiengesellschaft Köhle mbH*, 972 F.2d 1272, 1280-81 (Fed. Cir. 1992). Although the specification may be used to determine the

meaning of terms used in the claims, the specification may not be used as prior art. See *e.g.*, *In re Vogel*, 422 F.2d 438 (C.C.P.A. 1970).

Applicants respectfully submit that claims 64-67 of the '843 application, which are directed to compounds of formula (V), do not render obvious the claimed compounds of formula (I) of the subject application. In particular, Applicants submit that the compounds of formula (I) are not obvious over the compounds of formula (V), because formula (V) requires that at least one of R^{30} , R^{31} or R^{32} is present and is a therapeutic agent, and there is no teaching or suggestion in the claims of the '843 application of a compound without a conjugated therapeutic agent. Moreover, claims 64-67 of the '843 application do not teach or suggest a compound within the scope of the presently claimed invention. The present claims, including new claims 66-71, are directed to compounds which are not recited to be conjugated to a therapeutic agent, whereas the claims of the '843 application recite compounds which are conjugated to a therapeutic agent.

Thus, Applicants respectfully submit that claims 1, 5, 19-20, 22-26, 30-31, 34-39, 55, 58-59 and 66-71 are patentably distinct from claims 64-67 of the '843 application.

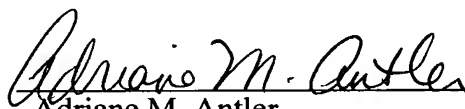
For the above reasons, Applicants respectfully request withdrawal of the double patenting rejection.

CONCLUSION

Applicants respectfully request that the present remarks be made of record in the instant application. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: May 15, 2007


Adriane M. Antler 32,605
JONES DAY (Reg. No.)
222 East 41st Street
New York, NY 10017
(212) 326-3939